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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/643,595	08/22/00	BARBERA-GUILLEM E	B-29

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EXAMINER	
ROARK, J	
ART UNIT	**PAPER NUMBER**
1644	3

DATE MAILED: 07/05/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Offic Action Summary	Application No. 09/643,595	Applicant(s) BARBERA-GUILLEM ET AL.	
	Examiner Jessica H. Roark	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-17 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-17 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892) ✓
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 2 . ✓
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Provisional application 60/152,498 (9/2/99) appears to provide adequate written support for the instant claims. Provisional application 60/150,256 (8/23/99) was not available to the Examiner. Thus the priority date of the instant claims appears to be at least 9/2/1999.

2. Applicant's IDS, filed 8/22/00 (Paper No. 2), is acknowledged.

3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention *to which the claims are directed.* Applicant is requested to delete the reference to compositions from the Title.

4. The formal drawings submitted 8/22/00 have been approved by the Draftsman.

5. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

6. Claims 1-17 are objected to because of the following informalities: Applicant is requested to amend the claims to recite "multiple sclerosis" rather than the abbreviation "MS".

7. Claims 2, 7, 11 and 15 are objected to because of the following informalities: the B cell phenotypes should be presented with each "+" as a superscript (e.g., $CD19^{+}sTn^{+}$). Appropriate correction is required.

8. Claim 4 is objected to because of the following informalities: the use of the Markush language "selected from the group consisting of" is confusing. It is suggested that Applicant consider simplifying the claim language by amending the claim to recite "...wherein the composition is administered parenterally, or in a site-directed method in which the composition...." Appropriate correction is required.

9. Claim 6 is objected to because of the following informalities:
a) the phrase "for reducing a" appears to be duplicated text and should be deleted;
b) in the phrase "*which* the composition is delivered into an access", "*wherein*" appears to be intended rather than "*which*". Appropriate correction is required.

10. Claim 14 is objected to because of the following informalities: the use of the Markush language "selected from the group consisting of" is confusing. Applicant should consider simplifying the claim language by amending the claim to recite "A method for treating an individual having multiple sclerosis (MS) and a pro-MS immune response, or having a pro-MS immune response;...."

11. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 2, 5, 7, 9, 11, 13-15 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

A) Claims 2, 7, 11 and 15 are indefinite for being in improper Markush format. The recitation of "and a combination thereof" as a member of the Markush group is improper because, as recited, elements are doubly included (See MPEP 2173.05(h)). The claim may be rewritten to recite "selected from the group consisting of mature B cells and memory B cells, $CD19^+sTn^+$ B cells, $CD19^+CD21^+sTn^+$ B cells, and $CD19^+CD5^+sTn^+$ B cells, or a combination thereof."

B) Claims 5, 9, 13 and 17 are indefinite for being in improper Markush format. The recitation of "and a combination thereof" as a member of the Markush group is improper because, as recited, elements are doubly included (See MPEP 2173.05(h)). The claim may be rewritten to recite "selected from the group consisting of one or more chemotherapeutic agents, an anti-inflammatory agent, a cytolytic agent, and a pharmaceutically acceptable carrier, or a combination thereof."

It is further noted that Applicant should also consider moving the recitation of "a pharmaceutically acceptable carrier" to the first mention of a composition in independent claims 1, 6, 10 and 14.

C) Claim 14 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the method comprising administering a composition.

Applicant should amend the claim to provide this step, as recited in claims 1, 6 and 10.

D) Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP 714.02 and 2163.06.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claim 1-2, 4-5, 10-11, 13-15 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Bhat et al. (US Pat No. 5,593,676, IDS; see entire document).

Bhat et al. teaches and claims a method of reducing an autoimmune response in an individual by administering parenterally a composition comprising an affinity ligand (anti-CDIM antibody) which selectively binds to a B cell determinant in an amount sufficient to deplete B cells and a pharmaceutically acceptable carrier (see entire document, including claims 1, 7 and 9; and especially page 7).

Bhat et al. teach that MS (multiple sclerosis) is an autoimmune disease (e.g. "Background" at pages 4-5).

Bhat et al. also teach that the B cell determinant targeted (CDIM) is found on substantially all peripheral B cells (e.g., page 6, 4th paragraph); therefore an affinity ligand which binds CDIM and depletes $CDIM^+$ B cells would inherently deplete mature B cells, memory B cells, $CD19^+sTn^+$ B cells, $CD19^+CD21^+sTn^+$ B cells and $CD19^+CD5^+sTn^+$ B cells, including those which are nonmalignant.

Finally, reduction in the inflammation underlying the clinical manifestations of MS would be an inherent property of any method that depleted B cells.

Applicant is reminded that no more of the reference is required than that it sets forth the substance of the invention. The claimed functional limitations would be inherent properties of a method of administering a CDIM affinity ligand to an individual. In addition, one of ordinary skill in the art would immediately envisage intravenous administration given a teaching of parenterally administration (see MPEP 2131.02).

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

16. Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Turk et al. (US Pat. No. 5,958,409) in view of Genain et al. (J Clin Invest 1995 96:2966-2974) and in further view of Anderson et al. (US Pat. No. 5,776,456, IDS).

The claims are drawn to a method for reducing a pro-MS immune response by administering an affinity ligand for a B cell determinant that depletes the targeted nonmalignant B cells, including an affinity ligand that is a chimeric anti-CD20 antibody.

Turk et al. teach and claim a method for treating multiple sclerosis (MS) by administering a therapeutically effective amount of a composition comprising an affinity ligand that is a chimeric antibody (see entire document, including claims).
Turk et al. also teach
administering a composition comprising the chimeric antibody in combination with a pharmaceutically acceptable carrier (e.g., claim 3 and bridging paragraph of columns 4 and 5);
administering the composition
in a site-directed method directly to the central nervous system (e.g., claims 4 and 5), or
by intravenous (i.e., parenteral) injection (e.g. column 7, especially lines 1-15);
further administering an additional component including a chemotherapeutic, anti-inflammatory, or cytolytic agent (e.g., column 7, especially lines 50-56).
Turk et al. also teach that although TNF-α has been implicated as an important effector molecule in MS, serum antibodies (i.e., the B cell-produced mediator of humoral immunity) are also important in producing the CNS pathology observed in MS (e.g. columns 2-3).

Turk et al. do not teach administering a composition comprising an affinity ligand that depletes targeted B cells, such as a chimeric anti-CD20 antibody.

Genain et al. teach that antibodies initiate the demyelination observed in MS; and that autoantibodies along with autoreactive T cells and inflammatory cytokines such as TNF-α are required for a fully developed MS lesions to occur (see entire document, especially Abstract and Discussion).

Anderson et al. teach the production of a chimeric anti-CD20 antibody and the use of this antibody to deplete nonmalignant B cells *in vivo* (see entire document, especially Examples II and III on pages 27-page 37). Anderson et al. also teach that CD20 is expressed early in B cell development and remains until plasma cell differentiation (e.g., page 8, 2nd full paragraph).

Given the teachings of Genain et al. that B cells initiate the demyelination observed in MS, and of Anderson et al. that a chimeric anti-CD20 antibody is useful in depleting B cells *in vivo*; the ordinary artisan at the time the invention was made would have been motivated to combine or substitute a method of B cell depletion to reduce or eliminate autoantibody production with the method of treating MS taught by Turk et al. Turk et al. teach using an anti-inflammatory anti-TNF-α chimeric antibody in combination therapies that target other aspects of the MS autoimmune process. In view of the teachings of Genain et al. that B cells produce autoantibodies that *initiate* pathology, the ordinary artisan would have had a reasonable expectation that depletion of the B cells that produce the pathogenic autoantibodies would reduce both the pro-MS immune response and the inflammation underlying the clinical symptoms of MS, especially if combined with other treatments. Further, Turk et al. provide a reasonable expectation that chimeric antibody therapy is an effective means of treating MS, and would therefore also be effective in reducing a pro-MS immune response. Anderson et al. teach that a chimeric anti-CD20 antibody efficiently depletes B cells *in vivo*; and given the expression of CD20 throughout B cell development the ordinary artisan would have reasonably expected that anti-CD20 therapy would deplete mature and memory B cells, $CD19^+sTn^+$ B cells, $CD19^+CD21^+sTn^+$ B cells and $CD19^+CD5^+sTn^+$ B cells, including nonmalignant B cells. In addition, targeting the pan B cell antigen CD20 would lead to a depletion of B cells irrespective of Ig specificity, and so would include B cells expressing immunoglobulins specific for antigens comprising a terminal alpha 2,6 linked sialic acid. Finally, routes of administration of a composition comprising chimeric antibodies for treatment of MS which affects the CNS are also taught by Turk et al, including both intravenous (i.e., parenteral) and intrathecally (i.e., in a site-directed manner by delivery into an access that directly supplies the central nervous system). Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jessica Roark, whose telephone number is (703) 605-1209. The examiner can normally be reached Monday to Friday from 8:00 to 4:30. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached at (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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July 5, 2001

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